REMARKS

Claims 1, 3, 14, and 43-50 constitute the pending claims in the present application.

To clarify the subject matter claimed, Applicants have amended claims 1 and 3. Support can be found throughout the specification, see, for example, the first object under "Summary of the Invention" section.

Applicants respectfully request reconsideration in view of the following remarks.

Claim rejections under 35 USC §103(a)

Claims 1, 3, 14, 43-49 are rejected under 35 U.S.C. 103 as being unpatentable over Girasole *et al.* in view of Kishimoto *et al.* (U.S. Pat. No. 5,888,510), for the reasons of record set forth at pages 2-4 of the previous Office Action (3/18/04).

Applicants reiterate that:

1) unlike Rheumatoid Arthritis, bone density is controlled *in vivo* by two types of counter-acting cells, osteoclast and osteoblast. The *in vitro* results of Girasole only teaches the effect of IL-11 signaling on osteoclast, but is completely silent about its effect on osteoblast. More importantly, it is completely silent about the unexpected discovery that IL-11 signaling has opposite effects in osteoclast and osteoblast *in vivo*, e.g., inhibiting IL-11 function simultaneously inhibits osteoclast function *and* enhances osteoblast function;

2) IL-11 signaling may not be significant enough to have an *in vivo* effect on bone density;

3) There is no motivation for a skilled artisan to predict IL-11 *in vivo* results from the results of an unrelated protein (IL-6) as described in Kishimoto.

Especially for point 1) above, there is simply nothing in the cited references that would teach or suggest to a skilled artisan that IL-11 would have opposite effects in two different type of cells (osteoclast and osteoblast) – in contrary, conventional wisdom would strongly suggest that the same cytokine (IL-11) would have the same or similar effects on different cell types (promoting osteoclast function – which is reducing bone density; and promoting osteoblast function – which is increasing bone density).

The Examiner held the view that bone formation and resorption are "a balancing process, which is constantly taking place in vivo," which is true. However, that would not automatically lead to the conclusion that a skilled artisan would expect an osteoclast inhibitor (as Girasole taught) would also be an osteoblast stimulator.

To support Applicants' argument, Applicants hereby submit a Rule 132 Declaration by inventor Dr. Shaughnessy. The Declaration indicated in paragraph 9 that the invention provides several unexpected results, including "treatment with an anti IL-11 antibody has the synergistic outcome of both enhancing bone formation (i.e. enhancing osteoblast activity) and decreasing bone resorption (i.e. inhibiting osteoclast activities). In this way, the disease can be not only halted but actually reversed in some cases. This provides an advantage over other treatments that just effect either osteoclast activity alone or osteoblast activity alone." (emphasis added)

Applicants respectfully remind the Examiner that the Supreme Court has articulated a standard whereby the PTO must establish a rational connection between the agency's fact-findings and its ultimate action. *Dickinson v. Zurko*, 119 S.Ct. 1816 (1999). In light of the inventor's Declaration and Applicants' arguments of record, and the presumption in favor of Applicants, it is respectfully asserted that the present rejection (agency adjudication) is not supported by "substantial evidence" from the Examiner, and as such, fails to rise above the "substantial evidence" test of Section 706(2)(D) of the Administrative Procedure Act (APA). At the minimum, the Office Action fails to pass the "arbitrary, capricious, an abuse of power, or otherwise not in accordance with law" standard set forth in Section 706(2)(A) of the APA. There is no reasonably acceptable logical reasoning based on sound fact finding, for the Office Action to insist that a skilled artisan would automatically believe an osteoclast inhibitor is *necessarily* an osteoblast stimulator, simply because these two cell types have opposite functions in controlling bone density.

Claim 50 is rejected under 35 U.S.C. 103 as being unpatentable over Girasole *et al.* (1995) in view of Kishimoto (supra) and Queen *et al.* (U.S. Pat. No. 5,530,101).

For the reasons above, the claimed invention is not obvious in view of Girasole and Kishimoto, and Queen does not in anyway correct these defects, even assuming a skilled artisan

would be motivated to combine Queen with Girasole and Kishimoto to make humanized antibodies to inhibit osteoclast function.

Pursuant to MPEP 2143, "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations."

Therefore, none of the three requirement for establishing a *prima facie* case of obviousness is met. Reconsideration and withdrawal of rejection under 35 U.S.C. 103(a) are respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

Date: September 27, 2004

Weishi Li
Reg. No. 53,217

Customer No: 28120
Docketing Specialist
Ropes & Gray, LLP
One International Place
Boston, MA 02110
Tel. 617-951-7000
Fax: 617-951-7050

Attorney Docket No. MDSP-P02-180 **PATENT**

Confirmation No. 9313

UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Stephen Shaugnessy et al.
Serial No. 09/491,982
Filed: January 27, 2000
For: OSTEOPOROSIS TREATMENT

Group Art Unit: 1646
Examiner: Mertz, Prema

Declaration Under 37 C.F.R. § 1.132

Stephen Shaughnessy states as follows:

1. I am the named inventor and applicant on the above application.

2. I reside at

72 Leaside Dr.
St. Catharines, Ontario
Canada, L8V 1C3

3. My formal education includes:

- Honours B.Sc. Brock University, 1982
- Masters (Biochemistry), Brock University, 1985
- Ph.D. (Medical Sciences), McMaster University, 1992
- Post-Doctoral Fellow, Dept. of Medicine, McMaster University, 1992-94

4. I am currently an Associate Professor in the Dept. of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario, Canada.

5. I have approximately 11 years of postdoctoral research experience.

6. My research has focused on the study of bone.

7. I am a member of The American Society for Bone and Mineral Research.

8. I have many publications in the field of osteogenesis. I have received a new investigators award from the Heart and Stroke Foundation of Canada as well as a Premiers Research Excellence Award.

9. I am a co-inventor along with Richard Carl Austin of the subject matter claimed in the application entitled "Osteoporosis Treatment" which was filed in the United States Patent and Trademark Office on January 27, 2000. The invention provides a novel method for the treatment and/or alleviation of symptoms of clinical conditions, such as osteoporosis, in which increased bone resorption or decreased bone formation is the underlying pathology, as described in the summary of the invention on page 3 of the application. According to the claimed method of the invention, the balance between bone resorption and bone formation is adjusted by administering an IL-11 antagonist, such as an antibody. This method provides several unexpected results as outlined below:

- IL-11 was shown to have an inhibitory effect on bone nodule formation as described in example 1 of the application. Furthermore, IL-11 antagonists were demonstrated to reverse the inhibitory effect of IL-11 on bone formation as demonstrated in example 6 and 7 of the application.

- We further demonstrated that anti IL-11 antibodies that are capable of interfering with the formation of tertiary complex of IL-11, IL-11 receptor, and GP 130 also inhibit osteoclast formation, thereby reducing the rate of bone resorption. This effect was shown both *in vitro* and *in vivo*.

- Our invention provides significant beneficial effects. We demonstrate that treatment with an anti IL-11 antibody has the synergistic outcome of both enhancing bone formation (i.e. enhancing osteoblast activity) and decreasing bone resorption (i.e. inhibiting osteoclast activities). In this way, the disease can be not only halted but actually reversed in some cases. This provides an advantage over other treatments that just effect either osteoclast activity alone or osteoblast activity alone.

- The cited art does not describe an effective treatment that enhances osteoblastic activity while inhibiting osteoclastic activity comprising administering an anti-IL-11 antibody to a patient.

- The examiner asserts that it would be obvious to combine the teachings of Girasole et al. and Kishimoto et al. to arrive at our invention.

- Girasole et al. demonstrate that under certain conditions IL-11 is an important cytokine for the development of osteoclasts. Girasole et al. also demonstrated that anti IL-11 antibodies inhibit 1,25(OH)2D3-stimulated osteoclast formation.

- Girasole did not describe any *in vivo* treatment with an anti-IL-11 antibody. Therefore, there was no way for him to determine if by targeting IL-11 one would either maintain or reverse the bone loss that is associated with estrogen deficiency. Indeed, bone mass is maintained by balancing bone formation with bone resorption and Girasole was completely silent on IL-11s role in bone formation. Furthermore, while Girasole does suggest that administration of an anti-IL-11 antibody can prevent or reduce the ability of several agents such as 1,25 $(OH)_2D_3$ or PTH to induce osteoclast formation *in vitro* he does not address the effect that an anti-IL-11 antibody would have on osteoclastogenous *in vivo*

where numerous growth factors, hormones and cytokines are all acting on the osteoclast and it's precursors in concert. Taken as a whole, it is not obvious from the Girasole reference that administration of an anti IL-11 antibody to a postmenopausal women would be an effective way to halt and/or reverse the systems of bone degeneration.

- Kishimoto et al. describe methods for inhibiting synovial cell growth and treating rheumatoid arthritis by administering an anti-IL6 antibody. This is a completely different disease and different antibody from my invention. As Girasole states on page 1516 in the second column, "The DNA structure and amino acid sequence of human IL-11 are completely distinct from those of human IL-6." Furthermore, on page 1518, second column, Girsole also reports that while anti-IL-11 antibodies could partially inhibit TNF or IL-1's ability to induce osteoclast formation, anti-IL-6 antibodies could not, suggesting that these cytokines can and do behave differently in bone.

- I do not believe that it would be obvious to someone working in my field to combine these two references and come to the conclusion that since anti IL-6 antibody is effective in rheumatoid arthritis, an anti IL-11 antibody would be useful in the treatment of postmenopausal osteoporosis as suggested by the examiner. Kishimoto never even mentions postmenopausal osteoporosis or IL-11. Girasole never suggests using an anti-IL-11 antibody would enhance bone formation while reducing bone resorption and he repeatedly states that IL-11 and IL-6 are very different cytokines with different properties. Thus, combining the two references would not lead to my invention.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are

punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued hereon.

Dr. S. Shaughnessy

Date: Sept 23/04

HAM_LAW\ 91412\1